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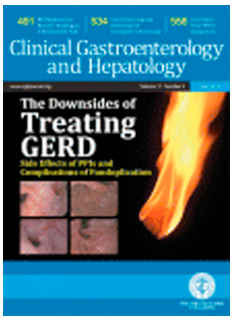

Impact of Inflammatory Bowel Disease Therapies on Durability of Humoral Response to SARS CoV-2 Vaccination

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Research Letter

Title: Impact of Inflammatory Bowel Disease Therapies on Durability of Humoral Response to SARS CoV-2 Vaccination

Short Title: Post-Vaccination Anti-Spike Titer Decay in IBD

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Abbreviations:

IBD, inflammatory bowel disease

TNF, tumor necrosis factor

VDZ, vedolizumab

UST, ustekinumab

IMM, immunomodulators

CS, systemic corticosteroids

GMT, geometric mean titer

CI, confidence interval

CRP, c-reactive protein

FCP, fecal calprotectin

EDC, exponentiated decay coefficient

Immunization against the spike protein of SARS-CoV-2 reduces transmission[1, 2] and severe outcomes. However, little is known regarding the impact of immune-mediated diseases and immunosuppressive medications on the efficacy of vaccination. Vaccination immunity is transient, with breakthrough cases increasing at longer time intervals since the last dose[3, 4]. While there are data on SARS-CoV-2 vaccine on early seroconversion in inflammatory bowel disease (IBD) patients[5], no data in the same cohort exist describing the durability of these antibodies over time. We sought to investigate the impact of IBD and its therapies on post-vaccination antibody response and kinetics of immunogenicity decline, as these findings may better inform clinical guidelines and recommendations on precautions and booster vaccination.

Within a prospectively followed cohort of 195 patients with IBD who underwent one Anti-S Total Ab titer test at a non-predetermined time, between April 15th and October 19th 2021, 185 had measured titers following both doses of the BNT162b2 (Pfizer, BioNTech; 60%, n=111) or mRNA-1273 (Moderna; 35.1%, n=65) vaccines, and 9 (4.6%) the JNJ-78436735 vaccine (Janssen Pharmaceutical Companies; excluded from analyses due to low sample size). All vaccine doses were given at recommended dosing intervals. We divided the patients into two main medication groups: vedolizumab (VDZ)/ustekinumab (UST)/Mesalamine/Budesonide/No therapy as **Group 1** and those on anti-TNF-α ± Immunomodulators (IMM) as **Group 2**. There were seven patients on corticosteroids (prednisone ≥20mg/day or equivalent within 30 days of dose 1) and seven on tofacitinib, which we excluded from main analyses given low sample sizes. VDZ, UST, and Mesalamine/Budesonide/No therapy were grouped together to improve sample size since antibody titer trends between all three were similar on preliminary analysis (**Supplementary Figure 1A**). Furthermore, there was no difference in testing interval distribution between VDZ/UST and

mesalamine/budesonide/No Therapy. Median time between dose #2 and titer measurement was 126 days (IQR 89-162), similarly distributed between mRNA vaccines (p=0.799) and within vaccine-medication groups (p=0.403; **Supplementary Figure 1B**). Among 169 mRNA-vaccine recipients, 46 had qualitative results (>2500 u/mL, >250 u/mL, <0.4 u/mL) and were included only in dichotomous analyses. We included patients with quantitative titers without prior history of COVID-19 (n=121) in titer decay analyses. Geometric mean titer (GMT) of Anti-S Total Ab amongst all patients was 306 u/mL (95% Confidence Interval [CI] 234-401). The overall mean $\log_e$(Anti-S Total Ab) was 5.72 (95%CI 5.45-5.99) without significant differences between vaccines (BNT162b2 5.83±1.61 vs. mRNA-1273 5.67±1.51; t-test p=0.6). One breakthrough COVID-19 infection was observed in a 69-year-old with severely active Crohn's disease treated with infliximab, three weeks after a titer of 13 u/mL (measured 57 days after BNT162b2 dose #2). Patient characteristics and peri-vaccination disease activity approximated by surrogate markers (Albumin, C-Reactive Protein, Fecal Calprotectin) are described in **Supplementary Table 1.**

Comparisons of mean $\log_e$(Anti-S Total Ab) across subgroups revealed significant differences between medication Groups 1 and 2, in both BNT162b2 and mRNA-1273 recipients (**Figure 1A**). Comparisons among four arbitrarily-selected titer thresholds, at different timepoints and overall, showed significantly lower proportions of patients in Group 2 that mounted Anti-S Total Ab above each threshold, with statistically significant difference persisting up to Anti-S Total Ab ≥ 300 u/mL for at least 4 months after dose #2, while comparisons after 6 months exhibited large numerical differences without reaching statistical significance due to sample size (**Figure 1B**).

There was significant decay observed in Group 2 (n=42, exponentiated decay coefficient [EDC] 1.8%/day, p=0.012; estimated half-life 38 days) and it was significantly faster (Δ-slope p=0.045) than Group 1 (n=74, p=0.058, EDC 0.05%/day, estimated half-life 153 days), as shown in **Figure 1C.**

Figure 1D shows the differences between the two mRNA vaccines among patients receiving anti-TNF-α antagonist monotherapy**,** with graphical evidence of greater decay in BNT162b2 (n=25, EDC 2.4%/day, p=0.002, half-life 28 days) compared to mRNA-1273 (n=10, EDC 0.9%/day, p=0.188; half-life 76 days), and slope difference approaching significance (p=0.109), despite relatively low sample size.

Four patients (2.3%, mean age 63.3 years) had undetectable antibodies (measurement days: 7, 34, 104, 181; three BNT162b2, one mRNA-1273). Two of the BNT162b2 patients (one on ustekinumab) and the mRNA-1273 patient (on ustekinumab and 6-mercaptopurine) were also receiving tacrolimus after solid-organ transplant. The fourth patient (BNT162b2, titer at day #181) was on adalimumab and on dialysis for ESRD.

These data demonstrate robust immunogenicity among IBD patients to SARS-CoV-2 vaccination, with the notable exception of those on simultaneous transplant immunosuppressants, and are the first data to describe the kinetics of immunogenicity decay in this cohort. While our cohort had only one vaccinated patient develop COVID-19, our breakthrough infection rate is likely underestimated as there was no predetermined testing at prespecified intervals, potentially missing asymptomatic carriers. Patients on anti-TNF-α ± immunomodulators had lower titers and more

rapid decay than those on no immunosuppression/vedolizumab/ustekinumab. Our findings are in line with the findings of Edelman-Klapper *et al.*[5], where at a 4-week follow-up period, anti-TNF-α patients exhibited significantly lower Anti-S IgG titers, together with lower neutralizing and inhibitory functions of Anti-S IgG, when compared to non-anti-TNF-α treated patients. Recent data by Aldrige *et al.*[6], utilizing the same titer assay, showed that a >500u/mL cutoff conferred 38% lower risk for breakthrough infection in the community setting (n=197/8858 [2.2%], median follow-up 4 months). Furthermore, earlier studies have shown that Anti-S antibodies correlate with both neutralizing antibody titers[7] and T-cell response[8], allowing extrapolation of the clinical usefulness of Anti-S antibodies in conferring immunity against SARS-CoV-2. Additionally, initial titer response has been suggested to positively impact long-term immunity[9]. The above, and together with our findings, suggest that the majority of IBD patients still carry a theoretical risk of breakthrough infection after vaccination, but especially those on Anti-TNF-α agents (<20% with Anti-S Total Ab ≥500u/mL at ≥2 months after dose #2), Furthermore, among the anti-TNF-α-treated patients, titer decay was 2.7 times faster in BNT162b2 vaccine recipients compared to the mRNA-1273 vaccine, thus potentially exposing to earlier breakthrough-infection risk. We thus agree that augmented vaccine dosing regimens as recommended by CDC[10], may be needed for IBD patients, especially those on anti-TNF-α agents and possibly BNT162b2 recipients, although more data are needed to confirm the latter.

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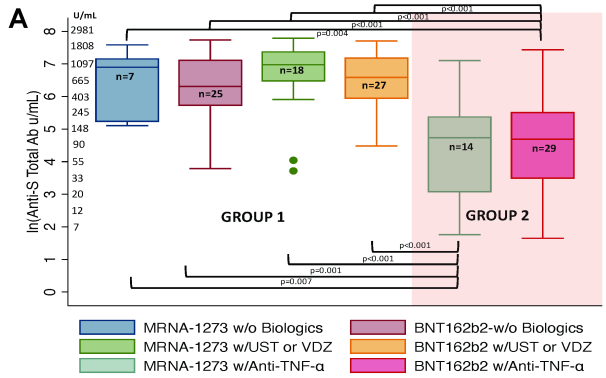
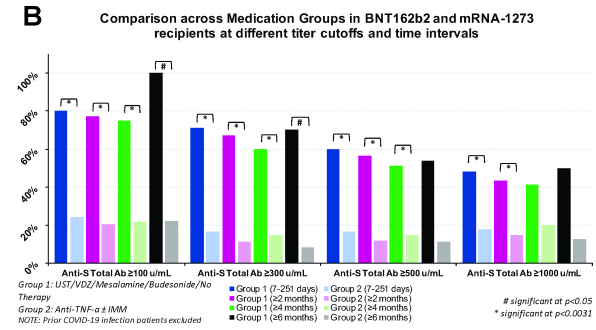
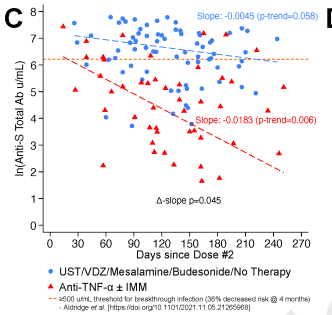
Legends:

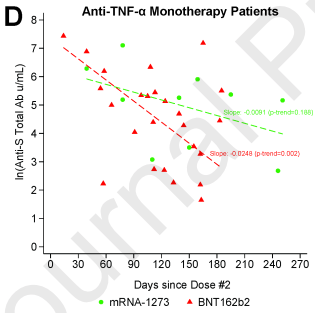
Figure 1.

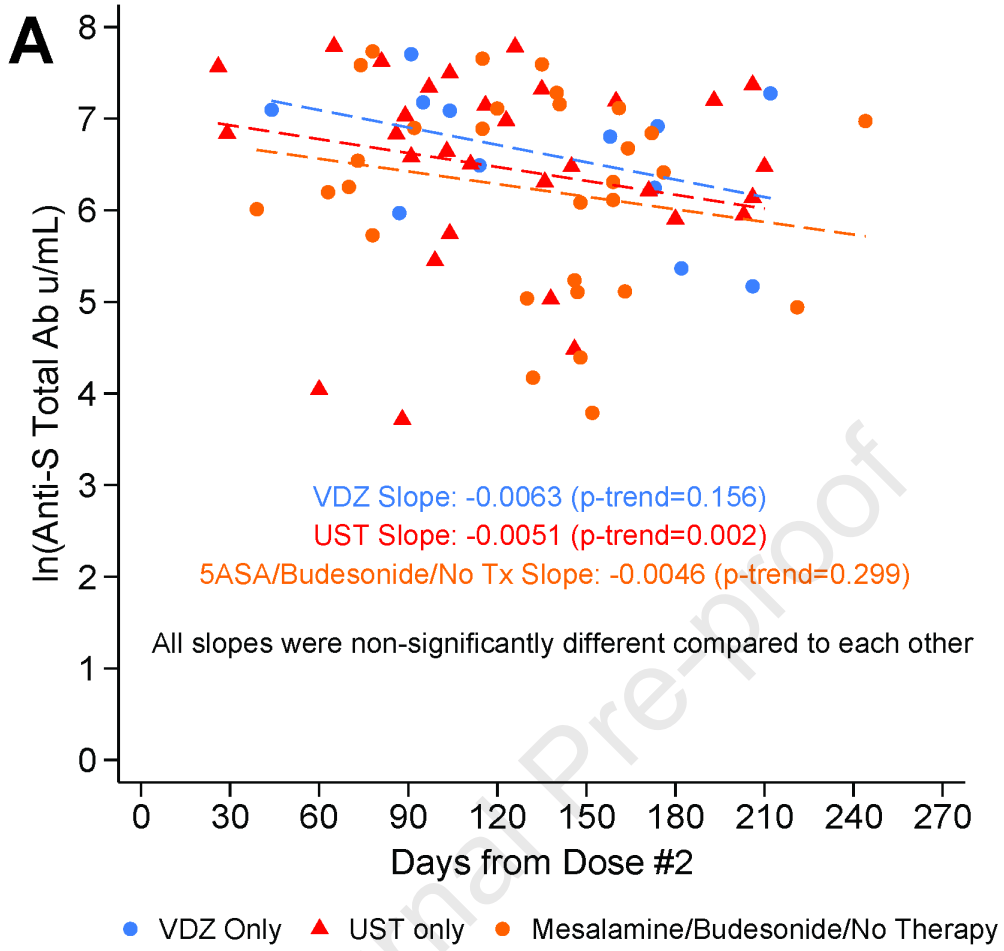
Panel A: Titer Comparison across medication-vaccine groups in BNT162b2 and mRNA-1273 recipients with IBD
One-way ANOVA of $\log_e$(Anti-S Total Ab) means across the groups revealed significant difference between medication groups 1 and 2, in both BNT162b2 and mRNA-1273 recipients
Panel B: Comparison across Medication Groups in BNT162b2 and mRNA-1273 recipients with IBD at different titer cutoffs and time intervals
Comparisons among four arbitrarily-selected titer thresholds at different timepoints and overall, showing significantly lower proportions of patients in Group 2 mounting an Anti-S Total Ab titer above each threshold, with statistically significant difference persisting up to Anti-S Total Ab ≥ 300 u/mL for at least 4 months after dose #2, while comparisons after 6 months exhibited large numerical differences without reaching statistical significance due to sample size.
Panel C: BNT162b2 and mRNA-1273 Recipients with IBD (excluding prior COVID-19)
Robust linear regression lines fitted for each medication group. Group 1 (VDZ/UST/mesalamine/budesonide/no therapy) showed a near-significant decreasing trend. Group 2 (Anti-TNF-α/CS/IMM) had significant linear decay in ln(Anti-S Total Ab), and significantly faster than Group 1. Most patients in Group 1 were below the 500 u/mL (orange-dotted line) threshold for breakthrough infection protection, as described by Aldridge *et al* (2021).
Panel D: Patients on Anti-TNF-α Antagonists (excluding IMM/CS/prior COVID-19)
Robust linear regression lines fitted for each vaccine group, among patients exclusively on Anti-TNF-α antagonists. Both vaccines had significant linear decay in ln(Anti-S Total Ab).
IBD, Inflammatory Bowel Disease; VDZ, vedolizumab; UST, ustekinumab; TNF, tumor necrosis factor; IMM, immunomodulators.

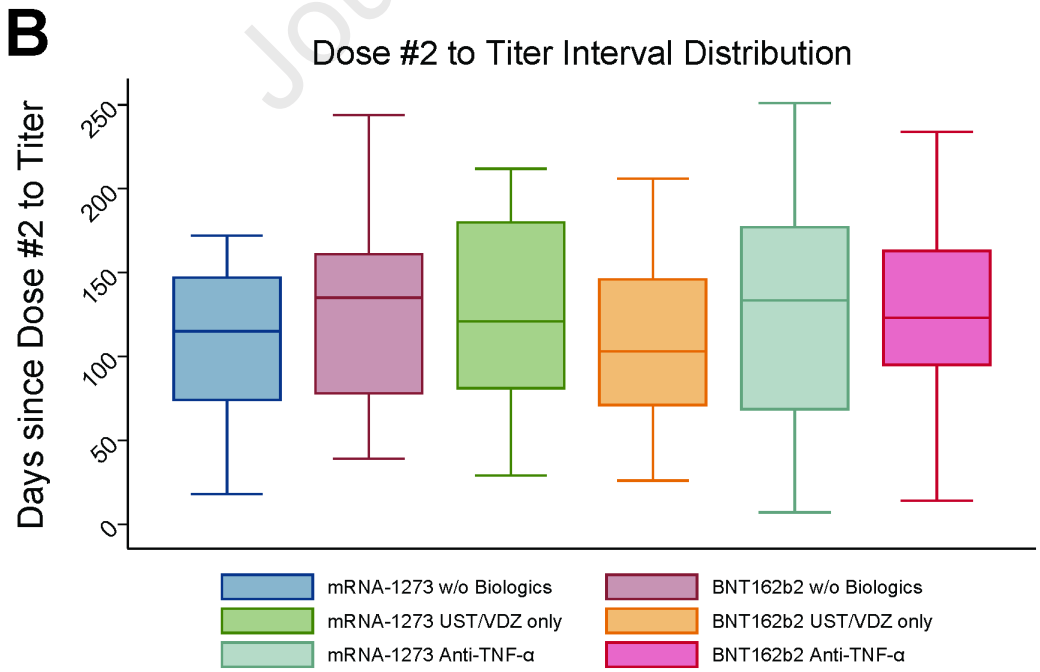












Supplementary Text

Methods

Data was collected retrospectively using the DataMart Inflammatory Bowel Disease (IBD) database of NewYork-Presbyterian Hospital-Weill Cornell Medicine, from April 1st 2021 to October 19th 2021. We collected all patients with IBD who had "SARS-CoV-2 Semi-Quantitative Total Antibody Spike" test (LabCorp test #164090, an electrochemiluminescence immunoassay). The data was then quality-controlled via manual chart review. The study was approved by the Institutional Review Board.

Missing values were not imputed due to sample size limitation (n=185), to ensure data validity. Continuous variables were analyzed using the t-test and Mood's medians test for normally and non-normally distributed data, respectively. Categorical variables were analyzed using chi-square or Fisher-exact tests. Multiple comparisons were done using one-way ANOVA, with Bonferroni correction to adjust for alpha-error inflation. The main outcome of interest, Anti-S Total Ab titer, was presented as a geometric mean titer or log-transformed (with base *e*), given its log-normal distribution and to allow linear modelling on its otherwise non-normally distributed residuals should be left untransformed. Robust linear regression, which is robust to potential outliers and thus allowing to include all available data, was used to fit linear trends among various comparison groups to assess the linear ln(Anti-S Total Ab) decay since dose #2 of vaccination. By extension, the exponentiated decay coefficients represent the % change from the geometric mean titer. STATA MP 15 was used for all analyses (StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC). All comparison were deemed significant *a-priori* at $p<0.05$, unless otherwise stated.

Supplementary Table 1. Characteristics of IBD patients who received mRNA-vector vaccines

Variable	mRNA-1273 n=65 (36.9%)	BNT162b2 n=111 (63.1%)	Overall n=176	p-value
	[n (%) or mean ± SD, median; IQR]			
Age at Dose #1 (years)	47.5 ± 17.4 (43; 33-63)	47.1 ± 15.3 (47; 33-59)	47.3 ± 16.0 (47; 33-60.5)	0.890
Female	42 (64.6)	77 (69.4)	119 (67.6)	0.515
Prior history of COVID-19	6 (9.2)	10 (9)	16 (9.1)	0.961
Crohn's Disease	43 (66.2)	69 (62.7)	112 (64)	0.648
Ulcerative Colitis Extent				
- E1	1 (4.6)	(0)	1 (1.6)	
- E2	9 (40.9)	20 (50)	29 (46.8)	0.345
- E3	12 (54.6)	20 (50)	32 (51.6)	
Ulcerative Colitis Severity				
- S0	3 (13.6)	7 (17.5)	10 (16.1)	
- S1	8 (36.4)	15 (37.5)	23 (37.1)	0.971
- S2	4 (18.2)	6 (15)	10 (16.1)	
- S3	7 (31.8)	12 (30)	19 (30.7)	
Crohn's Disease Classification				
- A1	5 (11.6)	10 (14.7)	15 (13.5)	
- A2	23 (53.5)	49 (72.1)	72 (64.9)	0.026
- A3	15 (34.9)	9 (13.2)	24 (21.6)	
- L1	10 (23.3)	27 (39.7)	37 (33.3)	0.073
- L2	8 (18.6)	11 (16.2)	19 (17.1)	0.741
- L3	25 (58.1)	30 (44.1)	55 (49.6)	0.150
- L4	2 (4.7)	1 (1.5)	3 (2.7)	0.314
-B1	17 (100)	30 (96.8)	47 (97.9)	0.454
- B2	18 (100)	20 (95.2)	38 (97.4)	0.348
- B3	11 (100)	20 (95.2)	31 (96.9)	0.462
- Perianal Disease	7 (100)	12 (92.3)	19 (95)	0.452
Biologics/SM within 3 months of Dose #1				
- No Biologic/SM	20 (30.8)	35 (31.5)	55 (31.3)	
- IFX/ADA/CTZ	14 (21.5)	33 (29.7)	47 (26.7)	
- UST	22 (33.9)	25 (22.5)	47 (26.7)	0.474
- VDZ	6 (9.2)	14 (12.6)	20 (11.4)	
- Tofacitinib	3 (4.6)	4 (3.6)	7 (4)	
Prednisone ≥20mg/day within 30 days of 1st dose	4 (6.2)	3 (2.7)	7 (4)	0.258
Immunomodulators	11 (16.9)	7 (6.3)	18 (10.2)	0.025
Anti-TNF-α + IMM	2 (14.3)	2 (6.1)	4 (8.5)	0.355
Vaccination-related Data				
- Above Median Anti-S Total Ab (≥477 u/mL)	46 (70.8)	66 (59.5)	112 (63.6)	0.132
- Vaccine Non-Responder	1 (1.5)	3 (2.7)	4 (2.3)	0.617
- Titer Testing Interval (days since Dose #2)	131 ± 60 (145; 81-174)	124 ± 51 (123; 91-161)	126 ± 54 (126; 89-162)	0.441
- Anti-S Total Ab Titer (u/mL) [n=128]	759.8 ± 713.0 (GM: 340) (593; 107-1256)	610.6 ± 601.8 (GM: 291) (445; 140-982)	659.6 ± 641.5 (GM: 305) (477; 125-1107)	0.225
- ln(Anti-S Total Ab) Titer (u/mL) [n=128]	5.83 ± 1.61 (6.38; 4.67-7.14)	5.67 ± 1.51 (6.10; 4.94-6.88)	5.72 ± 1.54 (6.17; 4.82-7.01)	0.661
Disease Activity Markers				

Any Albumin <3.5 mg/dL (from 60 days prior to dose #1 up to titer date)	15 (25.4)	15 (16.3)	30 (19.9)	0.171
Mean Albumin (g/dL; from 60 days prior to dose #1 up to titer date) [n=151]	3.91 ± 0.45 (3.9; 3.7-4.2)	4.06 ± 0.47 (4.2; 3.85-4.4)	4.00 ± 0.47 (4.1; 3.8-4.3)	0.042
Any FCP ≥ 250 µg/g (from 60 days prior to dose #1 up to titer date)	16 (57.1)	17 (50)	33 (53.2)	0.575
Mean FCP (µg/g; from 60 days prior to dose #1 up to titer date) [n=62]	397.2 ± 471.2 (291; 77-492)	447.1 ± 671.6 (205; 43-437)	424.6 ± 585.6 (239; 66.5-486)	0.741
Any CRP ≥1 mg/dL (from 30 days prior to dose #1 up to titer date)	18 (40)	12 (16.4)	30 (25.4)	0.004
Mean CRP (mg/dL; from 30 days prior to dose #1 up to titer date) [n=59]	1.02 ± 1.84 (0.4; <0.04-1.3)	0.68 ± 1.72 (<0.04; <0.04-0.4)	0.81 ± 1.77 (<0.04; <0.04-0.80)	0.309

SD, standard deviation; IQR, interquartile range; SM, small molecule; IFX, infliximab; ADA, adalimumab; CTZ, certolizumab; UST, ustekinumab; VDZ, vedolizumab; Anti-S, Anti-Spike; ln, natural logarithm; FCP, fecal calprotectin; GM, geometric mean; CRP, C-Reactive Protein.

Supplementary Legends

Supplementary Figure 1A: Days since Dose #2 Among Non-Anti-TNF-α Medication groups
Preliminary analysis of slopes and intercepts (i.e., theoretical immediate post-vaccination titers) were non-significantly different between UST-only, VDZ-only and Mesalamine/Budesonide/No Therapy groups.

Supplementary Figure 1B: Days since Dose #2 Distribution between Vaccine-Medication Groups
The median time between second dose and titer measurement was 126 days (IQR 89-162) and similarly distributed between mRNA vaccines (p=0.799) and within vaccine-medication groups (p=0.403).
IFX, infliximab; ADA, adalimumab; CTZ, certolizumab; UST, ustekinumab; VDZ, vedolizumab